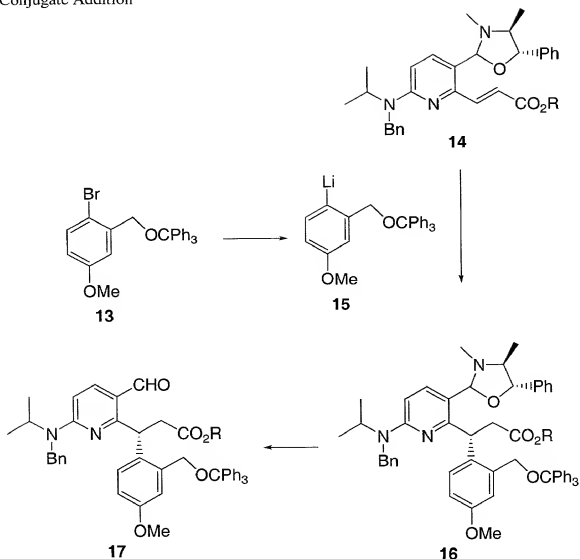


REACTION SCHEME D

Conjugate Addition



R = (C₁-C₆)-alkyl

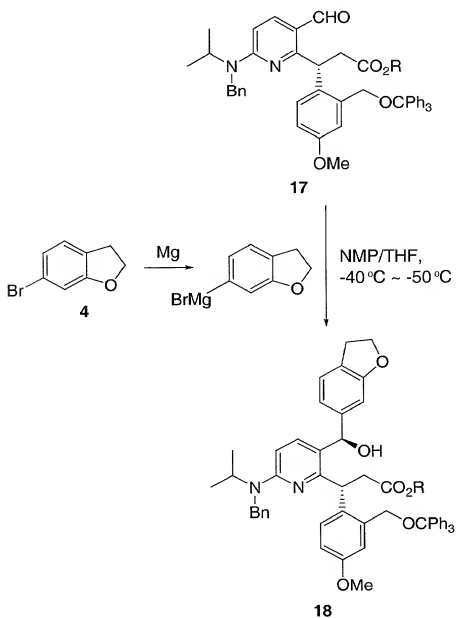
5

- Compound (15) reacts with the α,β -unsaturated ester bearing a pseudoephedrine (14) or alternatively N-methyl-cis-aminoinanol chiral auxiliary, in an aprotic solvent or a mixture thereof (preferably THF/toluene) at a temperature of about -80°C to about 0°C , preferably about -78°C to about -50°C . Work up the reaction mixture with acid and water (to remove the auxiliary) at a temperature between about -15°C and about 10°C affords compound (17) in high yield and good selectivity. It is noted that other chiral auxiliary groups can be utilized in this
- 10

asymmetric addition. (See WO 98/06698, published by the World Intellectual Property Organization on February 19, 1998.)

REACTION SCHEME E

5 Grignard Addition



R = (C₁-C₆)-alkyl

In Reaction Scheme E, addition of a Grignard reagent (prepared from the aryl bromide and magnesium) to the compound (17) in a mixture of THF/NMP at about -80°C to about 30°C (preferably about -40°C to about -50°C) affords compound (18) in quantitative yield and good diastereoselectivity. Addition of additives and/or selection of solvent may enhance the selectivity as shown in Tables 3, 4 and 5.

Table 3: The Effect of Additive on Grignard Addition of (17)
(R is *tert*-butyl)

Additive	MgBr ₂ •Et ₂ O	LiBr	BF ₃ •Et ₂ O	ArLi	ZnCl ₂	DMPU
Selectivity	7.6/1	6.7/1	5.3/1	1.8/1	NR	6.0/1

Adding about 2.5 equivalents of MgBr₂•Et₂O slows down the reaction but increases the selectivity to about 7.6/1. Similarly, about two equivalents of LiBr also slows down the reaction with slight increase of the selectivity (6.7/1, 50% conversion).

Compared to MgBr₂•Et₂O and LiBr, addition of BF₃•Et₂O and DMPU (about 5 equivalents) results in low-conversion without much improvement in selectivity.

Table 4: The Effect of Solvent on Grignard Addition of (17)
(R is *tert*-butyl)

Solvent	THF	toluene	DMF	NMP	(1:1) NMP/THF
T (°C)	-78	-78	-60 to RT	-20 to -10	-40 to -50
Selectivity	5/1	5.6/1	NR	15/1	25/1

As shown in Table 4, a non-polar solvent such as toluene fails to improve the selectivity (5.6/1), whereas a polar solvent such as

N-methylpyrrolidone (NMP) considerably enhances the selectivity (15/1). A mixed solvent of (1:1) NMP:THF at about -40°C to about -50°C even further enhances the selectivity resulting a cleaner reaction with improved stereoselectivity (25/1).